REMARKS

The Examiner has stated that a translation of the foreign priority document is required to gain the benefit of the foreign priority date. A verified translation of the foreign priority document accompanies this amendment. Accordingly, applicants are entitled to the benefit of the foreign priority date.

Claim 1 stands rejected under 35 USC 102(b) as being anticipated by Arora. Claim 1 also stands rejected under 35 USC 102(b) as being anticipated by Bungard. This claim has been cancelled. Accordingly, this rejection is now moot.

Claims 2-8 stand rejected under 35 USC 103(a) as being unpatentable over Ozaki in view of Bungard and Koishihara. This rejection is respectfully traversed.

Applicants claim a therapeutic agent that includes: (1) interferon-α or interferon-γ, and (2) an antibody that specifically binds to a protein having the amino acid sequence as set forth in SEQ ID NO: 2, and that has a cytotoxic activity."

The Examiner states that Ozaki teaches that anti-HM1.24 Moab can be used for immunotherapy of multiple myeloma. However, this reference does not suggest the use of interferon-α and interferon-γ as claimed. Specifically, in the claimed invention the cytotoxicity is enhanced by increasing the amount of antigen expressed on the surface of the target cells. As can be scene from the last part of Example 1 of the present invention, the presence of interferon-α and interferon-γ enhances the amount of expressed antigen HM1.24 on the surface of various cancer cells. Since therapeutic effect corresponds with the amount of the antigen on the cell surface, by increasing the amount of the antigen, interferon-α and interferon-γ enhances the therapeutic effect of the claimed agent.

The Examiner relies upon Bungard as disclosing: "ADCC of mAb 17-1A and the mAB BR55-2 against the colorectal carcinoma is enhanced by the treatment of cytokines including interferon-α and interferon-γ and IL-2." However, this reference, along with all the other references

cited by the Examiner, fails to disclose any advantage for administering interferon-α and interferon-γ in combination with the claimed antibody. Specifically, the references fail to disclose the synergistic effects of these substances. With out knowledge of this synergistic effect, one of ordinary skill in the art would not be motivated to make the specifically claimed combination.

In addition, Bungard does not show the use of interferon-α and interferon-γ for enhancing antibody-dependent cell-mediated cytotoxicity (ADCC), which is the basis of the claimed invention. Specifically, in Fig. 1 Bungard discloses the effect of cytokines such as interferon-α and interferon-γ on the number of cancer cells, and shows that the number of the cancer cells is not changed. Fig. 1 does not refer to the enhancement of the expression of any antigens of the cells (see, the central paragraph on page 214, "Direct effect of cytokines and mAb on HT29 cells").

Further, Figs. 2 and 3 of Bungard test the concentration dependent effect of various cytokines on ADCC activity (see, "Effect of single cytokines on ADCC", page 215). None of this data shows a significant difference that is dependent on the presence or absence of an antibody (difference between "Tu + PBMC" and "Tu + PBMC + BR55-2", and difference between "Tu + PBMC" and "Tu + PBMC + 17-1A"). Accordingly, in these figures, most of the effect is "antibody-independent cell-mediated cytotoxicity", and not "antibody-dependent cell-mediated cytotoxicity".

In Fig. 4 on page 217 the effect of a combination of three cytokines is shown. The figure shows that most of the effect is derived from antibody-independent activity (see, Fig. 4 does not show any difference between A and B). Similarly, the remainder or the figures do not show the result in an antibody-independent condition.

Accordingly, the above data does not provide any motivation to use cytokines for increasing ADCC activity, which is the basis of the present invention.

Koishihara is cited by the Examiner to show that anti-HM1.24 "has cytotoxic activity that bonds to SEQ ID NO:2 of the instant invention." Koishihara, however, like the other

references, fails to disclose administering interferon-α and interferon-γ in combination with the claimed antibody or any motivation for administering this claimed combination.

Since, as described above, the references cited by the Examiner alone or in combination fail to anticipate or render obvious the claimed combination of interferon-α and interferon-γ, the rejection of claims 2-8 should be withdrawn.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing Attorney Docket No. 350292001300.

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